EDA Assessment Report for Biological Medicinal Product

(Scientific Discussion)

Group A and C Meningococcal Polysaccharide Vaccine

Neisseria meningitidis group A capsular polysaccharide 50 mcg/0.5ml
Neisseria meningitidis group C capsular polysaccharide 50 mcg/0.5ml

Date: November 2024

Unit: Technical Assessment Unit

Assessment report

Group A and C Meningococcal Polysaccharide Vaccine

Administrative information:

Invented name of the medicinal product:	Group A and C Meningococcal Polysaccharide Vaccine
INN (or common name) of the active substance(s):	• Neisseria meningitidis group A capsular polysaccharide 50 mcg/0.5ml • Neisseria meningitidis group C capsular polysaccharide 50 mcg/0.5ml
Marketing Authorization holder	Yuxi Walvax Biotechnology co. Ltd. No. 83 South Dongfeng Road, High and New Technology Industries Development Zone, Yuxi city, Yunnan Province - CHINA
Applied Indication(s):	indicated for active immunization for the prevention of invasive meningococcal disease caused by Neisseria meningitidis serogroups A and C. It I s approved for use in persons 2 years of age and older. It is not indicated for the prevention of meningitis caused by microorganisms other than N. meningitidis serogroups A and C. It is neither indicated for treatment of meningococcal infections
Pharmaceutical form(s) and strength(s):	- lyophilized powder for reconstitution for s.c injection -50 mcg/0.5ml
Route of administration	Subcutaneous injection

Approved pack(s):	Finished product: Carton box containing 18 plastic trays. Each plastic tray containing 420 labelled vials and pamphlet only. Each tray should contain cover. Lyophilized Product is packed in neutral borosilicate glass vial with chlorobutyl rubber stopper and aluminum-plastic cap. Diluent: Carton Box containing 18 plastic trays. Each plastic tray contains 420 labelled vials and pamphlet only. Each tray could contain cover. Diluent is packed in neutral borosilicate glass vial with chlorobutyl rubber stopper and aluminum-plastic cover.

List of abbreviations

CTD	Common technical document
PP	Polypropylene
USP	United States Pharmacopeia
GMP	Good manufacturing practice
Sop	Standard operating procedure

Dossier initial submission and evaluation process.

- The product was submitted for registration via 343/2021 ministerial decree.
- The dossier evaluation by the registration administration units was started on 13.9.2023 after providing all the required documents according to the "Checklist for documents of new biological products registration file".
- Full CTD along with detailed SOPs were provided.

Table of contents

1. General introduction about the product including brief description of the AI, its mode of action and indications

-Men AC Injection is available as - Group A meningococcal bulk polysaccharide: colorless or pale yellow, odorless, clear liquid.
The bulk polysaccharide contains group A meningococcal antigen and traces of proteins and nucleic acid from group A meningococcus. The bulk polysaccharide can show immunoreaction against group A meningococcus specific antibody.
Group C meningococcal bulk polysaccharide: colorless or pale yellow, odorless, clear liquid.
The bulk polysaccharide contains group C meningococcal antigen and traces of proteins and nucleic acid from group C meningococcus. The bulk polysaccharide can occur immunoreaction against group C meningococcus specific antibody
-The composition of the drug product consists of:

About the product

For Group A Meningococcal Polysaccharide:
N. meningitidis group A polysaccharide consists of partly O-acetylated repeating units of Nacetylmannosamine, linked with 1α→6 phosphodiester bonds.
For Group C Meningococcal Polysaccharide:
N. meningitidis group C polysaccharide consists of partly O-acetylated repeating units of sialic acid, linked with 2α→9 glycosidic bonds.

2. Quality aspects:

2.1 Introduction

2.2 Drug Substance (Active ingredient)

- **General information**

International non-priority name	**Common name**
N. meningitidis group A polysaccharide	Group A Meningococcal Polysaccharide
N. meningitidis group C polysaccharide	Group C Meningococcal Polysaccharide

- **Manufacture, process controls and characterization:**

Manufacturer:
- Men AC is manufactured Yuxi Walvax Biotechnology Co., Ltd

Description of Manufacturing Process and Process Controls.
- The description of each stage in manufacturing process of MEN AC drug substance, flow chart, quantity of used material, operating parameter, in process control and the percentage yield had been submitted in the file
- The flow chart for each stage represents the in-process control and typical yield ranges is also illustrated in the file.

Control of Materials
-Sufficient information on raw materials used in the active substance manufacturing process has been submitted.

-All raw materials are sourced from qualified suppliers. Raw materials are received, identified, tested and released according to written Standard Operating Procedures (SOPs) as required by cGMP.
-Materials used in the manufacture of drug substance are tested internally and accepted on the basis of relevant pharmacopeia testing methods & Supplier's Certificate of Analysis with reference to internal specifications.

Controls of Critical Steps and Intermediates

Process parameter and the Critical quality attribute for the manufacturing process stages had been identified. Information on the quality control of the intermediate had been submitted with description of the acceptance criteria of tests and process parameter.

Process Validation

- active substance manufacturing process has been validated adequately.
- Tests results of critical quality attribute and results for critical parameter attribute in each stage of men ac drug substance manufacturing had been demonstrated, aligned with the pre-determined acceptance criteria and show production process consistency.

Manufacturing Process Development.

- The submitted manufacturing process development summarizes the development of men ac mentioned in file.

- **Characterization**

The phosphate group and the O- acetyl group are the important antigenic determinants of the A group meningococcal capsule polysaccharide. Therefore, the phosphorus content and the O-acetyl content are the key control index of the A group meningococcal capsule polysaccharide as their content has great influence on the immunogenicity of A polysaccharide.
The content of sialic acid and the content of O- acetyl are the key indicators of the quality control of the group C capsule polysaccharide as their content has a great influence on the immunogenicity of C polysaccharides.

Impurities and their Limits in Polysaccharide Purification Process

Nucleic acid, protein and endotoxin are the main impurities in refined polysaccharide production. Impurities Testing Results during Process Development shows residual nucleic acid, protein and endotoxin contents in two serogroups of polysaccharides, which are all within the limit, indicating the purification process can effectively remove the impurities of nucleic acid, protein and endotoxin

- **Specification**
  The release specification for the active substance comprises tests for physical characters, identity, purity and impurities, potency, quantity, microbiological attributes and general attributes.
- **Analytical Procedures**
  SOP List for Meningococcal Polysaccharide and Meningococcal Bulk Polysaccharide is summited in MA file
- **Batch analysis**
  Commercial batches representing process validation analyses data were submitted and their results comply with specification sheet and defined acceptance criteria.

- **Reference Standards or Materials**

Information regarding the reference standards used is sufficient. With respect to method validation, sufficient validation data for methods have been provided.

Container closure system

- The meningococcal bulk polysaccharide is stored in 2 L polypropylene (PP) NALGENE bottles.
- Intermediate polysaccharide:

The meningococcal polysaccharide is stored in 15 mL polypropylene (PP) Centrifugal tube.

Stability of drug substance

Approved Shelf Life of bulk saccharides: 12 months
Intermediate polysaccharide: 24 months
Approved Storage Condition of bulk polysaccharides: stored at -20°C
Intermediate polysaccharide: -20°C

2.3 Drug product:

-Description and Composition of the Drug Product:

Lyophilized vaccine looks like a white crisp cake, after reconstitution with diluents as the stated value, it immediately turned into a clear solution free of foreign matters.

- Pharmaceutical Development

Components of drug product

Excipients

Name	Supplier	Standard	Function
Sodium chloride (pharmaceutical grade)	MERCK	Chinese Pharmacopoeia, International Pharmacopeia	Maintain osmotic pressure
Lactose	MEGGLE	Chinese Pharmacopoeia	Protectant of lyophilization

- Formulation Development

The composition of the drug product was selected to match exactly the formulation of the reference products. No own formulation development was performed but followed the reference product formulation.

- Physicochemical and Biological Properties

All tests are included in file

- Manufacturing Process Development

Critical process parameters are illustrated and including Strain amplification, Fermentation, Crude polysaccharide preparation, Purification of polysaccharide, Final bulk preparation, Finished product preparation.

- Microbiological Attributes

This product is sealed packages of sterile lyophilized powder. The stability results showed that the packaging can fully guarantee that products not be contaminated by microorganisms during the validity period.

- **Compatibility**

The following control tests have been performed and the results were satisfied Appearance, Polysaccharide content, Molecular size and Bacterial endotoxin.

Manufacture of the drug product:

Description of manufacturing process and process controls along with manufacturers and responsibilities.

Manufacturer:

-The finished product manufacturing and batch release take place at Yuxi Walvax Biotechnology Co., Ltd No. 83 South Dongfeng Road, High & New Technology Industries Development Zone, Yuxi, Yunnan Province, China

- Control of critical steps and intermediates

The critical steps of the men ac drug product manufacturing process along with the associated in-process tests and acceptance criteria are listed in the dossier.

- Process validation and / or evaluation

-A Process validationprotocol & report of Manufacturing of Group A and C Meningococcal Polysaccharide Vaccine is provided in the file

- A concurrent Commercial-scale Process Verification Report for Drug Product of Group A and C Meningococcal Polysaccharide Vaccine is provided in the file. -The results of all production steps are valid.

- **Product specification:**

- Specifications of drug product and diluent are provided in tabular form with brief reference to the method used.

-The specifications include physical characters, general tests, tests for identity, tests for purification, activity, quantity, tests for contaminants.

- Justification of the drug product specifications at the release and during stability studies are provided.

- Excipients included in the drug product are lactose and sodium chloride, which are tested on as per Chinese Pharmacopoeia and International Pharmacopeia

-These components are controlled and tested to the standards appropriate for their intended use and function.

-The excipient of animal-origin used in the production of Group A and C Meningococcal Polysaccharide Vaccine is lactose.

- **Reference Standards or Materials.**

List of Reference Standards or Materials used and their manufacturers are tabulated in the CTD file.

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- **Container closure system**

-Container closure system primary packaging Neutral borosilicate glass vial with Halogenated butyl rubber stopper for lyophilized sterile powder (chlorination), Halogenated butyl rubber stopper for injection (chlorination), Aluminium-plastics combined caps

-Secondary packaging: For Finished product, Carton box containing 18 plastic trays. Each plastic tray containing 420 labelled vials and pamphlet only. Each tray should contain cover.
For Diluent: Carton Box containing 18 plastic trays. Each plastic tray contains 420 labelled vials and pamphlet only. Each tray could contain cover
Group label on each tray of the product and the diluent showing product name, composition, batch number, manufacturing date, expiration date, indication, Reg No., storage conditions, barcode, precautions, etc.

Stability of the drug product
Approved Shelf Life: 24 months
Approved Storage Conditions: Store at 2°C - 8°C

3. Non –clinical aspect:

- **group A and C meningococcal polysaccharide vaccine** is a lyophilized Meningococcal capsular polysaccharide of group A and C, indicated for active immunization for the prevention of invasive meningococcal disease caused by Neisseria meningitidis serogroups A and C. It is approved for use in persons 2 years of age and older. It is not indicated for the prevention of meningitis caused by microorganisms other than N. meningitidis serogroups A and C. It is neither indicated for treatment of meningococcal infections.
- **Toxicology:** The nonclinical study of Men AC polysaccharide vaccine is mainly dependent on toxicology evaluation that includes Animal allergenic study, Acute and abnormal toxicity studies, Subcutaneous stimulation test, Active systemic anaphylaxis test and Passive cutaneous anaphylaxis test.

▪Allergenic study conducted on guinea pigs showed normal weight increase and no abnormal reaction i.e., the vaccine does not contain any allergen. ▪Acute and abnormal toxicity studies conducted on mice showed no obvious abnormal symptoms and all animals remained healthy and survived, with increase of body weight during the observation period.
▪Subcutaneous stimulation test conducted on white rabbits showed that all rabbits had no swelling, congestion, induration or other local reactions at the injection site. Also, all groups had no abnormal macroscopic subcutaneous tissue and muscle gross anatomy at injection site. Histopathological examination showed slight irritation with both low and high vaccine dosage. On the 16th day after injection, the aforementioned irritation completely recovered.
▪Active Systemic Anaphylaxis and Passive Cutaneous Anaphylaxis test results showed that the vaccine was basically free of allergens and did not cause specific immune responses that cause tissue injury or physiological dysfunction in guinea pigs.

- **Overall conclusion:** Data presented by toxicology studies performed, supports that this vaccine has good animal safety. Overall, the application is approvable from the non-clinical point of view.

1. **Clinical aspect:**

The clinical development program for group A and C meningococcal polysaccharide vaccine included: Phase I clinical trial (an open, uncontrolled, safety observation study, **which preliminarily evaluated the safety** of vaccine in healthy subjects aged 2 and above.) **and Phase III clinical trial** (randomized, blinded and controlled with the similar domestic product, **to evaluate the safety and immunogenicity** of group A and C meningococcal polysaccharide vaccine, freeze-dried in healthy children over 2 years of age), the company then conducted a post-marketing **Phase IV clinical trial** using single center, open, uncontrolled clinical trial design, **to evaluate the post-approval large scale production safety and immunogenicity** among healthy children and adults.

Clinical Efficacy:
Immunogenicity:
-The Group A and C Meningococcal antibody sera of all the subjects (include susceptible subjects and non-susceptible population) are significantly elevated to different levels.

-**Phase III clinical trial** showed that: all subjects (susceptible and non-susceptible) that were immunized with meningococcal group A and C polysaccharide vaccines had significant increase of serum antibody of group A and C to various extent. In study groups, the antibody positive rate was 97.80% and 96.52%, and overall antibody GMT was 1:322.54 and 1:671.33, respectively, indicating an average increase of 68.38 and 141.83 times that before immunization.

-Post-immunization antibody seroconversion (4-fold increase) rate among study group, control group, and different age groups showed non-statistically significant differences.

-In the post-marketing **phase IV** clinical trials, 231 subjects of 2-6 years-old in immunogenicity subgroup were observed with post-immunization antibody seroconversion / 4-fold increase rate of group A being 98.70%, and that of group C was 96.10%. The antibody seroconversion rate / 4-fold increase rate in these subjects after full immunization were similar to that observed in Phase III clinical trial.
-The antibody response level was different in different age group.

Clinical Safety:

-There was no SAE observed related to the studied vaccine, with sorely 5 subjects were found with
fever ≥40℃, headache, diarrhea, allergic reaction and level 4 hysteria.

-The different reaction rate of local, systemic reaction, and moderate, severe reaction in test group and control group was non-significant.

-Based on the above clinical data, the Group A and C Meningococcal Polysaccharide Vaccine produced by Yuxi Walvax has demonstrated good safety and immunogenicity outcomes, which is capable of effectively preventing epidemic cerebrospinal meningitis caused by group A and C meningococcus.

Benefit/risk conclusion

- **In conclusion the overall benefit/risk of men ac is favorable in the following:**

for active immunization for the prevention of invasive meningococcal disease caused by Neisseria meningitidis serogroups A and C. It I s approved for use in persons 2 years of age and older. It is not indicated for the prevention of meningitis caused by microorganisms other than N. meningitidis serogroups A and C. It is neither indicated for treatment of meningococcal infections

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.